CLASSIFICATION S-E-C-R-E-T SECRET
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REPORT
CD NO.

50X1-HUM

COUNTRY	USSR	DATE OF INFORMATION	1951
SUBJECT	Scientific - Chemistry, organophosphorus compounds		
HOW PUBLISHED	Bimonthly periodical	DATE DIST. 10	Mar 1952
WHERE PUBLISHED	Moscow	NO. OF PAGES	9
DATE PUBLISHED	Jul/Aug 1951		
LANGUAGE	Russian	SUPPLEMENT TO REPORT NO.	

THIS IS UNEVALUATED INFORMATION

SOURCE Izvestiya Akademii Nauk SSSR, Otdeleniye Khimicheskikh Nauk, No 4, 1951, pp 409-416.

COMBINED ANHYDRIDES OF CARBOXYLIC ACIDS AND DIETHYLPHOSPHOROUS ACID

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[The line of investigation pursued by this group at the institute in question closely touches upon the synthesis of compounds having cholinesterase inhibitor (nerve gas) activity. While the physiological properties of the substances synthesized in this instance are not known, the results of the work, when utilized with that aim in view, would advance research on the preparation of toxic organophosphorus compounds.]

In 1932, A. Ye. Arbuzov and B. A. Arbuzov (1) prepared the ethyl ester of pyrophosphorous acid for the first time by the action of bromine on the sodium salt of diethylphosphorous acid and studied its properties. The esters of pyrophosphorous acid were found to be highly reactive. They are anhydrides of dialkylphosphorous acids and possess a symmetrical structure with two trivalent phosphorus atoms:

$$(AlkO)_2P\text{-}O\text{-}P(OAlk)_2$$

On further investigation of the properties of these compounds, it was found that they enter into reaction with organic acids. Thus, the action of monobasic carboxylic acids -- isobutyric, butyric, isovaleric, crotonic, caproic, benzoic, and toluic -- on the ethyl ester of pyrophosphorous acid yielded compounds which were found to be combined anhydrides of diethylphosphorous acid and the corresponding carboxylic acid of the general type $RCOOP(OC_2H_5)_2$.

This interaction takes place with the evolution of heat and the decomposition of the ethyl ester of pyrophosphorous acid into diethylphosphorous acid and the combined anhydride, according to the equation:

$$RCOOH + (C_2H_5O)_2P\text{-}O\text{-}P(OC_2H_5)_2 = (C_2H_5O)_2\ POH + RCOOP(OC_2H_5)_2$$

The constants of the combined anhydrides obtained in this way are cited in the appended table.

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All of the compounds obtained according to the scheme cited above boil at higher temperatures than diethylphosphorous acid; therefore, their separation from the latter presents no difficulties. Only in the case of the combined anhydride of acetic and diethylphosphorous acids does the boiling point of the product nearly coincide with that of diethylphosphorous acid. The total mixture of reaction products in this case distills off within the range of 3 deg, as a result of which the combined anhydride could not be isolated in the pure form. Its presence in the mixture, however, was proven by the action of water (elevation of temperature) and sulfur. In the latter case, after the addition reaction was completed, the combined anhydride of acetic acid and the diethyl ester of thiophosphoric acid were isolated:

$$RCOO-\underset{\underset{S}{|}}{P}-(OC_2H_5)_2$$

The obtained combined anhydride was a colorless, mobile liquid, easily decomposed by moisture of the air. It distilled in vacuum without decomposition.

Like the esters of pyrophosphorous acid, the mixed anhydrides are also very reactive. Under the action of water, they decompose into diethylphosphorous acid and the carboxylic acid, according to the following equation:

$$RCOOP(OC_2H_5)_2 + H_2O = RCOOH + HOP(OC_2H_5)_2$$

The decomposition reaction is accompanied by a considerable evolution of heat. Thus, the action of 0.17 ml of water on 2.3 g of the combined anhydride of benzoic and diethylphosphorous acids raised the temperature of the mixture from room temperature to 117°. For derivatives of aliphatic acids the heat evolution is considerably lower.

The decomposition of a combined anhydride yields constant boiling-point mixtures of diethylphosphorous acid and the carboxylic acid in equimolecular proportions. It was observed that these azeotropic mixtures distill over within the range of one to 2 deg and that their boiling points are higher than that of either component separately. For example, the boiling point of butyric acid is 163° and of diethylphosphorous acid, 184°-186° or 70°-71° at 10 mm. A mixture of these in equimolecular proportions has a boiling point of 78°-79° at 12 mm.

These azeotropic mixtures were observed only in the case of aliphatic acids but not in the case of aromatic acids. The formation of constant boiling-point mixtures of diethylphosphorous and aliphatic acids was verified by individually conducted experiments.

Alcohol, like water, decomposes combined anhydrides. In this case, the reaction could be expected to proceed in two directions with the formation of four substances:

$$\text{I.}\quad C_2H_5OH + RCOOP(OC_2H_5)_2 = RCOOH + (C_2H_5O)_3P$$

$$\text{II.}\quad C_2H_5OH + RCOOP(OC_2H_5)_2 = RCOOC_2H_5 + (C_2H_5O)_2POH$$

The experiments showed that the reaction proceeds according to equation I.

The combined anhydrides, as compounds containing a trivalent phosphorus atom, react with copper monohalides with the evolution of heat, forming crystalline molecular compounds (the Arbuzov reaction).

Combined anhydrides add sulfur to form the corresponding compounds:

$$RCOOP(OC_2H_5)_2 + S = RCOOP(S)(OC_2H_5)_2$$

The substances obtained from the addition reaction are liquids which distill in a high vacuum with considerable decomposition, as a result of which it is difficult to isolate them in the pure form.

The action of ethyl iodide would be expected to convert the combined anhydrides into compounds containing a pentavalent phosphorus atom (Arbuzov isomerization) in which the isomerization reaction must be accompanied by the splitting off of the alkyl halide or the acyl halide:

I. $RCOOP(OC_2H_5)_2 + C_2H_5I = RCOO\text{-}P(C_2H_5)(OC_2H_5)_2 \rightarrow RCOO\text{-}P(=O)(C_2H_5)(OC_2H_5) + C_2H_5I$ (I)

II. $RCOOP(OC_2H_5)_2 + C_2H_5I = [RCO]O\text{-}P(C_2H_5)(OC_2H_5)_2 \rightarrow C_2H_5PO(OC_2H_5)_2 + RCOI$ (I)

An investigation of the reaction products showed that the course of the reaction was more complex than the schemes cited above would indicate. Besides the isomerization products, which were obtained according to the first scheme and were, in their turn, combined anhydrides of the carboxylic acid and the monoethyl ester of ethylphosphonic acid, high boiling substances were also obtained. The latter were colorless, mobile liquids with a weak odor, distilling in a high vacuum with partial decomposition. Their nature is being clarified.

EXPERIMENTAL PART

The ethyl ester of pyrophosphorous acid was prepared according to the method of A. Ye. Arbuzov and B. A. Arbuzov (2) by the action of the chloride of diethylphosphorous acid on the sodium salt of diethylphosphorous acid: bp, 102.5°-103° at 10 mm; yield, ~60% of the theoretical.

Preparation of Combined Anhydrides

1. Action of Isobutyric Acid on the Ethyl Ester of Pyrophosphorous Acid

To 7.8 g of the ethyl ester of pyrophosphorous acid were added 2.6 g of isobutyric acid. The temperature rose from 20° to 38.5°. To bring the reaction to completion, the mixture was heated on a bath at a temperature of 100°-120° for 10 min, after which it was distilled in vacuum. At 10 mm, the whole mixture distilled in the interval 72°-86°. After several distillations, the following two main fractions were separated: fraction I, bp 70°-71° at 10 mm, 1 g, n_D^{20} 1.4082 (apparently diethylphosphorous acid); and fraction II, bp 86°-87° at 12 mm, 1.1 g, n_D^{20} 1.4212, d_4^{20} 1.0233.

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Found: P 15.32%, 15.37%

Calculated for $C_8H_{17}PO_4$: P 14.9%

The isolated combined anhydride is a colorless, mobile liquid easily soluble in ether, benzene, acetone.

2. Action of Butyric Acid on the Ethyl Ester of Pyrophosphorous Acid

In a distillation flask were mixed 9.8 g of the ethyl ester of pyrophosphorous acid and 3.4 g of butyric acid. The temperature of the mixture rose from 23° to 45°. After 10 min of heating on a bath at 120°, the mixture was distilled in vacuum. At 11 mm, the following two main fractions were separated: fraction I, bp 71°-74°, 3.9 g (diethylphosphorous acid); fraction II, bp 93.5°-94°, 2.0 g, n_D^{20} 1.4253, d_4^{20} 1.0289, found MR 51.71, calculated MR 52.15.

Found: P 15.02%, 14.80%

Calculated for $C_8H_{17}PO_4$: P 14.9%

3. Action of Isovaleric Acid on the Ethyl Ester of Pyrophosphorous Acid

Nine and seven tenths grams of the ethyl ester of pyrophosphorous acid were [illegible]ed with 3.8 g of isovaleric acid. The initial temperature of the mixture was 21°, but 2-3 min after mixing, the temperature rose to 44°. The reaction was brought to completion by heating the mixture on a bath at 100°, after which the reaction products were distilled in vacuum. The two following main fractions were separated at 11 mm: fraction I, bp 71°-72° (diethylphosphorous acid); fraction II, bp 100°-101°, 2.5 g, n_D^{20} 1.4266, d_4^{20} 1.0078, found MR 56.51, calculated MR 56.77.

Found: P 14.09%, 14.11%

Calculated for $C_9H_{19}PO_4$: P 13.95%

4. Action of Crotonic Acid on the Ethyl Ester of Pyrophosphorous Acid

When 9.4 g of the ethyl ester of pyrophosphorous acid were mixed with 3.1 g of crotonic acid, the crystals of crotonic acid slowly dissolved with a slight evolution of heat. After 15 min of heating in a bath at 110°-120°, the liquid was distilled in vacuum. At 10 mm, the following fractions were obtained: fraction I, bp 70°-71° (diethylphosphorous acid); fraction II, bp 103°-104°, n_D^{20} 1.4501, d_4^{20} 1.0575.

Found: P 15.29%, 15.32%

Calculated for $C_8H_{15}PO_4$: P 15.04%

Fraction II (103°-104° at 10 mm) was a dense, colorless liquid with a weak odor, easily soluble in benzene and acetone, less easily soluble in ether and gasoline.

5. Action of Caproic Acid on the Ethyl Ester of Pyrophosphorous Acid

From 7.7 g of the ethyl ester of pyrophosphorous acid and 3.6 g of caproic acid, after they had been mixed and the mixture had been distilled in vacuum, the following were obtained: diethylphosphorous acid and a fraction with bp 118°-119° at 11 mm, 2.5 g, n_D^{20} 1.4310, d_4^{20} 0.9917, found MR 61.08, calculated MR 61.39.

Found: P 12.83%, 12.68%

Calculated for $C_{10}H_{21}PO_4$: P 13.13%

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6. Action of p-Toluic Acid on the Ethyl Ester of Pyrophosphorous Acid

A mixture of 8.2 g of the ethyl ester of pyrophosphorous acid and 4.3 g of p-toluic acid reacted at room temperature with a slight evolution of heat. Upon agitation, the crystals of p-toluic acid slowly went into solution. Distillation in vacuum resulted in the isolation of diethylphosphorous acid and a fraction with bp 116° at 1 mm in a quantity of 3.5 g, n_D^{20} 1.5029, d_4^{20} 1.1001.

Found: P 12.44%, 12.48%

Calculated for $C_{12}H_{17}PO_4$: P 12.11%

The combined anhydride of p-toluic and diethylphosphorous acids is a colorless, mobile liquid, odorless, and easily soluble in benzene, ether, and acetone.

7. Action of Benzoic Acid on the Ethyl Ester of Pyrophosphorous Acid

To 8.8 g of the ethyl ester of pyrophosphorous acid were added 4 g of benzoic acid. After the crystals of benzoic acid had dissolved, the temperature rose by 9°. Distillation in vacuum yielded the following fractions: bp 72°-75° at 12 mm, 4.3 g (diethylphosphorous acid); and fraction with bp 124°-127° at 4 mm, 6.7 g. After a second distillation, the second fraction had bp 102°-103° at 1 mm, n_D^{20} 1.4974, d_4^{20} 1.1193.

Found: P 13.22%, 13.17%

Calculated for $C_{11}H_{15}PO_4$: P 12.81%

8. Action of Acetic Acid on the Ethyl Ester of Pyrophosphorous Acid

To 10.1 g of the ethyl ester of pyrophosphorous acid were added 2.3 g of acetic acid. The reaction was accompanied by evolution of heat. The temperature of the mixture rose quickly from 21° to 46°. After heating for 5 min on a water bath, the liquid was distilled in vacuum. At 11 mm, all the liquid distilled in the interval of 68°-71° in a quantity of 11.8 g, with n_D^{20} 1.4149.

Since the boiling point of pure diethylphosphorous acid is 71°-72° at 11 mm, while that of the obtained mixture was 68°-71° at 11 mm, the substances could not be separated. The presence of a combined anhydride of acetic and diethylphosphorous acids in the mixture was proved by the action of water (elevation of the temperature) and sulfur, in which case the corresponding compound was isolated (see below).

Reactions of Combined Anhydrides

1. Action of Water on the Combined Anhydride of Isovaleric and Diethylphosphorous Acids

a. To 2.7 g of the combined anhydride was added 0.22 ml of water. In a short time, the temperature of the mixture rose from 19° to 65°. After the reaction had terminated, the liquid was distilled in vacuum. The boiling point of the main fraction was 80°-81° at 11 mm, n_D^{20} 1.4075.

Found: P 13.24%, 13.27%

Calculated for ($C_5H_{10}O_2$ + $C_4H_{11}PO_3$): P 12.91%

b. Isovaleric acid in a quantity of 4.1 g and 5.53 g of diethylphosphorous acid were mixed and the mixture distilled in vacuum at different pressures. The main quantity distilled in the following intervals:

I. 84°-85° at 13.5 mm; n_D^{20} 1.4074

II. 87°-89° at 17 mm; n_D^{20} 1.4074

III. 123°-125° at 82 mm; n_D^{20} 1.4074

Analysis of the fraction with bp 87°-89° at 17 mm gave P 13.02%; analysis of the fraction with bp 123°-125° at 83 mm:

Found: P 12.91%

Calculated for ($C_5H_{10}O_2$ + $C_4H_{11}PO_3$): P 12.91%

2. Action of Water on the Combined Anhydride of Butyric and Diethylphosphorous Acids

a. In a distillation flask, 0.19 ml of water was added to 2.2 g of the combined anhydride. The temperature of the mixture rose from 25° to 73°. The mixture was distilled in vacuum, the portion distilling off being 2 g of a liquid with bp 76°-78° at 11 mm, n_D^{20} 1.4057.

Found: P 14.14%, 14.16%

Calculated for ($C_4H_8O_2$ + $C_4H_{11}PO_3$): P 13.71%

b. Butyric acid in the amount of 1.5 g and 2.3 g of diethylphosphorous acid were mixed and the mixture distilled in vacuum. The boiling point of the chief fraction was 78°-79.5° at 12 mm, n_D^{20} 1.4055. Thus butyric acid, like isovaleric, forms an azeotropic mixture with diethylphosphorous acid.

3. Action of Water on the Combined Anhydride of Benzoic and Diethylphosphorous Acids

To 2.3 g of the combined anhydride in a distillation flask, 0.17 ml of water was added from a micropipette. In a short time, the temperature of the mixture rose from room temperature to 117°. The mixture was distilled in vacuum. At 12 mm, a fraction with bp 70°-80° distilled off. At this point, the temperature of the vapors of the liquid being distilled rose rapidly to 130°, and the outlet tube of the flask became clogged with crystals. The distillation was stopped, whereupon the liquid remaining in the flask crystallized on cooling. The crystals were extracted with ether; the substance had a melting point of 114°-116°; after recrystallization from hot water, the melting point was 120°-121°. A test sample mixed with benzoic acid melted at the same temperature. Crystals of benzoic acid were obtained in the amount of 0.9 g (81% of theoretical). After a second distillation of the fraction with bp 70°-80° at 11 mm, 0.9 g of a substance with bp 70°-71° at 11 mm was obtained; n_D^{20} 1.4079; d_0^{20} 1.0711. According to the constants it was diethylphosphorous acid, of which 1.3 g should have been obtained by theory.

4. Action of Alcohol on the Combined Anhydride of Benzoic and Diethylphosphorous Acids

In a distillation flask, 1.2 g of absolute ethyl alcohol were added to 6.3 g of the combined anhydride. The temperature of the mixture rose from room temperature to 56°, while at the same time, needle-like crystals separated out.

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The mixture was distilled in vacuum. At 13.5 mm, there distilled off 3.3 g of a fraction with bp 50°-53°. The temperature of the vapors of the liquid rapidly rose to 130°, and the outlet tube became clogged with crystals. The liquid remaining in the flask crystallized on cooling. The crystals were extracted from the flask. Their melting point was 116°-118°. After recrystallization from water, both the ordinary test sample and one mixed with benzoic acid melted at 120°-121°. Crystals of benzoic acid were obtained in the amount of 2.3 g (74.2% of theoretical).

After redistillation of the fraction with bp 50°-53°, there were obtained 2.3 g of a substance with bp 50°-51.5° at 13.5 mm. According to the constants, the substance was the ethyl ester of phosphorous acid: n_D^{20} 1.4114; d_0^{20} 0.9629; found MR 42.84; calculated MR 43.02.

5. Action of Sulfur on the Combined Anhydride of Acetic and Diethylphosphorous Acids

Into a distillation flask were placed 6.9 g of the ethyl ester of pyrophosphorous acid, and 1.59 g of acetic acid were added. The mixture was heated for 10 min on a bath at 120°. Since the boiling point of the combined anhydride of acetic and diethylphosphorous acids coincides with that of diethylphosphorous acid, which is also obtained in this reaction, the mixture was not separated. After cooling, 0.85 g of flowers of sulfur were added to the mixture. At normal temperature, no reaction occurred, but when the mixture was heated to 120° (thermometer in the liquid), solution of the sulfur took place rapidly. On distillation in a vacuum the following fractions were obtained.

Fraction I. 70°-77° at 13 mm (diethylphosphorous acid)

Fraction II. 92°-102° at 13 mm

After redistillation, the second fraction had a boiling point of 93°-96° at 3 mm; constants: n_D^{20} 1.4511; d_0^{20} 1.5105.

Found: S 14.6%; P 14.9%, 14.84%

Calculated for $C_6H_{13}O_4PS$: S 15.09%; P 14.62%

The combined anhydride of acetic acid and the diethyl ester of thiophosphoric acid is a mobile liquid with a weak odor and yellow color. The substance is insoluble in water, but easily soluble in ether, alcohol, and benzene.

6. Action of Sulfur on the Combined Anhydride of Caproic and Diethylphosphorous Acids

When a mixture of 2.7 g of the combined anhydride and 0.36 g of flowers of sulfur was heated to 120° (the thermometer in the liquid) the greater part of the sulfur dissolved. There was 0.1 g of residue. Distillation in vacuum yielded a main fraction with bp 109°-113° at 2 mm, n_D^{20} 1.4508.

Found: S 11.51%, 11.43%

Calculated for $C_{10}H_{21}O_4PS$: S 11.94%

7. Action of Cuprous Chloride on the Combined Anhydride of Isovaleric and Diethylphosphorous Acids

Into a test tube containing 0.8 g of the combined anhydride was placed 0.35 g of cuprous chloride. The temperature of the mixture rose spontaneously from 18° to 52°. On heating the test tube on a bath to 160°, the major quantity

of cuprous chloride went into solution. The dense, transparent liquid was poured out along with the cuprous chloride which did not react. After the mixture had been allowed to stand for some time, a small quantity of well-formed crystals separated out from the liquid. These were isolated and pressed out between sheets of filter paper: mp 105°-106°.

Found: Cl 11.5%

Calculated for $C_9H_{19}O_4PCuCl$: Cl 11.04%

8. Action of Ethyl Iodide on the Combined Anhydride of Isovaleric and Diethylphosphorous Acids

A mixture of 6.8 g of the combined anhydride and 1 ml of ethyl iodide was heated in a sealed tube for 3 hr at 135°-142°. After the tube cooled, a slight decrease in the volume of the reaction liquid was observed. After additional heating for 1 hr at the same temperature, no change in volume had taken place. The contents of the tube were transferred to a distillation flask, ethyl iodide removed in vacuum, and the remaining liquid distilled. As a result of the first distillation, the following fractions were obtained:

Fraction I. 88°-105° at 11 mm 0.5 g

Fraction II. 90°-130° at 3 mm 2.5 g

Fraction III. 130°-168° at 3 mm 2.5 g

Residue 0.3 g

After several distillations of fractions II and III, the following two main fractions were separated:

I. 120°-122° at 11 mm 0.75 g, n_D^{20} 1.4312, d_0^{20} 1.0365

II. 150°-154° at 2 mm 1.2 g, n_D^{20} 1.4382, d_0^{20} 1.0974

Analysis of fraction with bp 120°-122° at 11 mm:

Found: H 8.37%; C 48.43%; P 14.21%, 14.22%

Calculated for $C_9H_{19}PO_4$: H 8.55%; C 48.6%; P 13.95%

Fraction II (bp 120°-122° at 11 mm) was a mobile liquid with a weak odor, insoluble in water but easily soluble in ether and benzene. Therefore, on the basis of the physical constants and analytical data, fraction II was the combined anhydride of isovaleric acid and the monoethyl ester of ethylphosphonic acid. The nature of fraction I has not been clarified.

CONCLUSIONS

1. By the action of isobutyric, butyric, isovaleric, crotonic, caproic, benzoic, and p-toluic acids on the ethyl ester of pyrophosphorous acid, combined anhydrides of the type $RCOOP(OC_2H_5)_2$ were prepared for the first time.

2. These combined anhydrides are capable of reacting and undergoing reactions characteristic of acid anhydrides.

3. Under the action of ethyl iodide, the combined anhydrides are isomerized (the Arbuzov reaction) into compounds with a pentavalent phosphorus atom $R\text{-}COOP(OC_2H_5)_2$ (O).

In addition, high-boiling substances, whose structures have not been clarified, are obtained.

BIBLIOGRAPHY

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2. A. Ye. Arbuzov and B. A. Arbuzov, Zhur Obshch Khim, Vol II, 1932, p 373

[Table follows.]

Formulas and Constants of Combined Anhydrides

No by Order	Formula	Bp in °C				n_D^{20}	d_4^{20}
1	$(CH_3)_2CH\text{-}COOP(OC_2H_5)_2$	86-87	at	12	mm	1.4212	1.0233
2	$CH_3\text{-}CH_2\text{-}CH_2\text{-}COOP(OC_2H_5)_2$	93.5-94	at	11	mm	1.4253	1.0289
3	$(CH_3)_2CH\text{-}CH_2\text{-}COOP(OC_2H_5)_2$	100-101	at	11	mm	1.4266	1.0078
4	$CH_3\text{-}CH{=}CH\text{-}COOP(OC_2H_5)_2$	103-104	at	10	mm	1.4501	1.0575
5	$n\text{-}C_5H_{11}\text{-}COOP(OC_2H_5)_2$	118-119	at	11	mm	1.4310	0.9917
6	$C_6H_5\text{-}COOP(OC_2H_5)_2$	102-103	at	1	mm	1.4974	1.1193
7	$p\text{-}CH_3\text{-}C_6H_4\text{-}COOP(OC_2H_5)_2$	116 125-125.5	at at	1 2.5	mm mm	1.5029	1.1001

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